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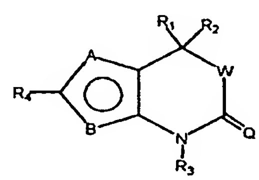

(I)

(57) Abstract

This invention provides compounds of formula (I) wherein A and B are independent substituents selected from S, CH or N; provided that when A is S, B is CH or N; and when B is S, A is CH or N; and A and B cannot both be CH; and when A and B both equal N, one N may be optionally substituted with a C_1 to C_6 alkyl group; R_1 and R_2 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A; or R^1 and R^2 are fused to form optionally substituted 3 to 8 membered spirocyclic alkyl, alkenyl or heterocyclic ring, the heterocyclic ring containing one to three heteroatoms selected from the group of O, S and N; or pharmaceutically useful salts thereof. The compounds of this invention are useful as agonists and antagonists of the progesterone receptor and in methods of inducing contraception and in the treatment or prevention of benign or malignant neoplastic diseases.

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CYCLOCARBAMATE AND CYCLIC AMIDE DERIVATIVES

Field of the Invention

This invention relates to compounds that act as agonists and antagonists of the progesterone receptor, their preparation, and utility.

Background of the Invention

Intracellular receptors (IR) form a class of structurally related genetic regulators known as "ligand dependent transcription factors" (R. M. Evans, *Science*, **240**, 889, 1988). The steroid receptor family is a subset of the IR family, including progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR).

The natural hormone, or ligand, for the PR is the steroid progesterone, but synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, have been made which also serve as ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex then translocates to the nucleus of the cell where it binds to a specific gene or genes present in the cell's DNA. Once bound to a specific DNA sequence the complex modulates the production of the mRNA and protein encoded by that gene.

A compound that binds to an IR and mimics the action of the natural hormone is termed an agonist, whilst a compound which inhibits the effect of the hormone is an antagonist.

PR agonists (natural and synthetic) are known to play an important role in the health of women. PR agonists are used in birth control formulations, typically in the presence of an ER agonist. ER agonists are used to treat the symptoms of menopause, but have been associated with a proliferative effect on the uterus (in non-hysterectomized women) which can lead to an increased risk of uterine cancers. Co-administration of a PR agonist reduces or ablates that risk.

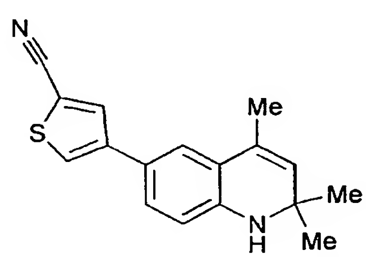
PR antagonists may also be used in contraception. In this context they may be administered alone (Ulmann, et al, *Ann. N. Y. Acad. Sci.*, **261**, 248, 1995), in combination with a PR agonist (Kekkonen, et al, *Fertility and Sterility*, **60**, 610, 1993) or in combination with a partial ER antagonist such as tamoxifen (WO 96/19997 A1 July 4, 1996).

PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz, et al, *Horm. Cancer*, 283, pub: Birkhaeuser, Boston, Mass., ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions such as fibroids (Murphy, et al, *J. Clin. Endo. Metab.*, **76**, 513, 1993) and endometriosis (Kettel, et al, *Fertility and Sterility*, **56**, 402, 1991).

PR antagonists may also be useful in hormone replacement therapy for post-menopausal patients in combination with a partial ER antagonist such as tamoxifen (US 5719136). PR antagonists such as Mifepristone have also been shown to have bone sparing effects in rodents, and as such may be useful in the treatment of osteoporosis associated with the menopause (Barengolts, et al, *Bone*, **17**, 21, 1995).

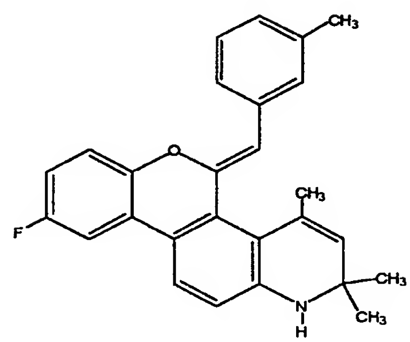
PR antagonists, such as mifepristone and onapristone, have been shown to be effective in a model of hormone dependent prostate cancer, which may indicate their utility in the treatment of this condition in men (Michna, et al, *Ann. N. Y. Acad. Sci.*, ***761**, 224, 1995).*

Jones, *et al*, (U.S. Patent No. 5,688,810) described the PR antagonist dihydroquinoline **1**.



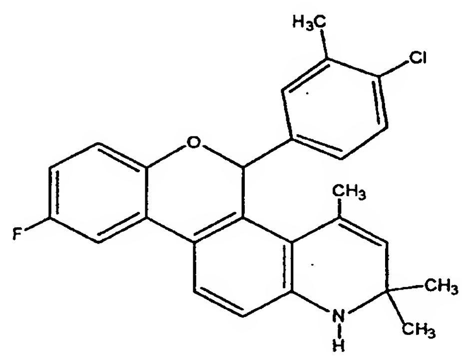
1

Jones, *et al*, described the enol ether **2** (U.S. Patent No. 5,693,646) as a PR ligand.



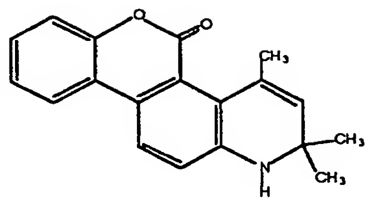
2

Jones, *et al*, described compound **3** (U.S. Patent No. 5,696,127) as a PR ligand.



3

Zhi, *et al*, described lactones **4, 5** and **6** as PR antagonists (J. Med. Chem., 41, 291, 1998).



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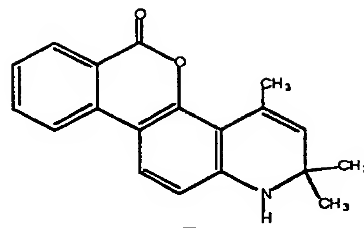

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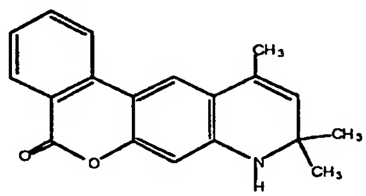
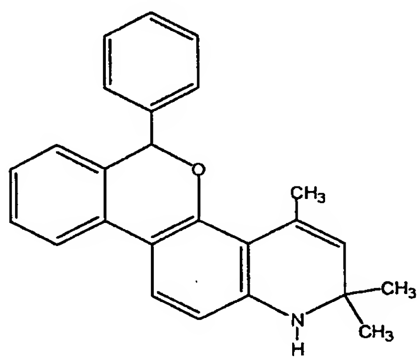


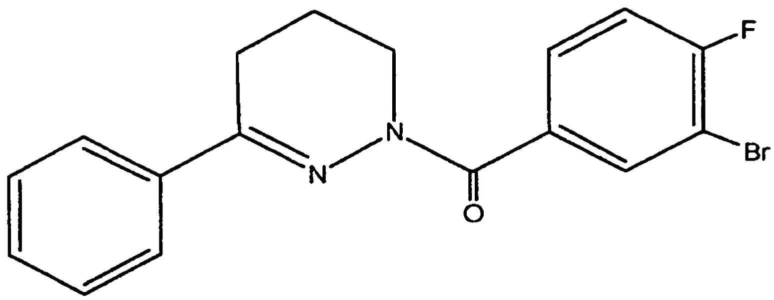
F

Zhi, *et al*, described the ether **7** as a PR antagonist (J. Med. Chem., **41**, 291, 1998).



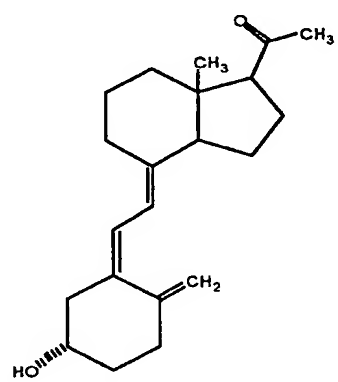
7

Combs, *et al.*, disclosed the amide **8** as a ligand for the PR (*J. Med. Chem.*, **38**, 4880, 1995).



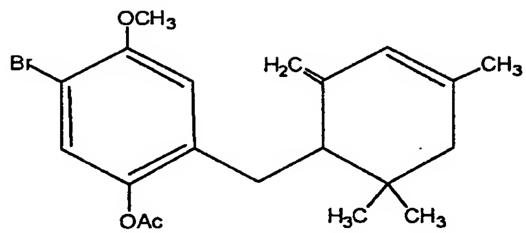
8

Perlman, *et. al.*, described the vitamin D analog **9** as a PR ligand (*Tet. Letters*, **35**, 2295, 1994).



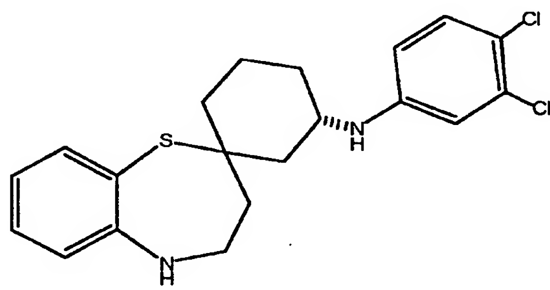
9

Hamann, *et al*, described the PR antagonist **10** (*Ann. N.Y. Acad. Sci.*, **761**, 383, 1995).



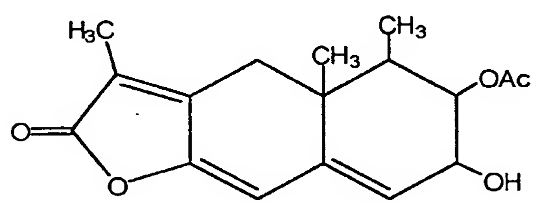
10

Chen, *et al*, described the PR antagonist **11** (Chen, et al, POI-37, 16th Int. Cong. Het. Chem., Montana, 1997).



11

Kurihari, *et. al.*, described the PR ligand **12** (*J. Antibiotics*, **50**, 360, 1997).



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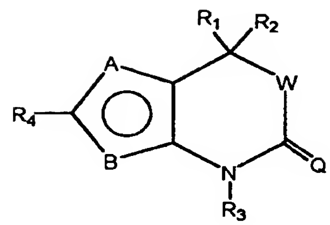
<u>**Description of the invention**</u>

This invention provides compounds of Formula I:



I

wherein:

A and B are independent substituents selected from S, CH or N;

Provided that when A is S, B is CH or N; provided that when B is S, A is CH or N;

and A and B cannot both be CH;

and when A and B both equal N, one N may be optionally substituted with an C_1 to C_6 alkyl group;

R_1 and R_2 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R^1 and R^2 are fused to form:

a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring, preferably a 3 to 6 membered spirocyclic alkyl ring; or

b) an optionally substituted 3 to 8 membered spirocyclic alkenyl ring, preferably a 3 to 6 membered spirocyclic alkenyl ring; or

c) an optionally substituted 3 to 8 membered spirocyclic ring containing one to three heteroatoms selected from O, S and N, preferably a 3 to 6 membered spirocyclic ring containing one to three heteroatoms;

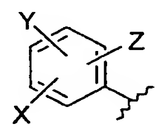
R^A is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, or COR^C;

R^C is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below,



X is selected from halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, $OCOR^D$, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independent independently selected from H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O S, SO, SO_2 or NR^5 and containing one or two independent substituents from the group including H, halogen, CN, NO_2 and C_1 to C_3 alkyl, C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, COR^F, or NR^GCOR^F;

R^F is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^G is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^5 is H, or C_1 to C_3 alkyl;

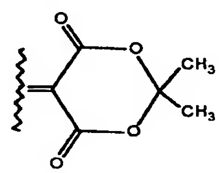
Q is O, S, NR^6, or CR^7R^8;

R^6 is from the group including CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, or SO_2CF_3;

R^7 and R^8 are independent substituents from the group including H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, or CN CO_2R^9;

R^9 is C_1 to C_3 alkyl;

or CR^7R^8 may comprise a six membered ring of the structure below:



W is O or a chemical bond

or a pharmaceutically acceptable salt thereof.

Among the preferred compounds of this invention are those of Formula I wherein:

A and B are independent substituents S, CH or N,

provided that when A is S, B is CH or N; and

when B is S, A is CH or N; and

A and B cannot both be CH; and

when A and B both equal N, one N may be optionally substituted with an C_1 to C_6 alkyl group;

R^1 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

R^2 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R^1 and R^2 are fused to form:

a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring; or

b) an optionally substituted 3 to 8 membered spirocyclic alkenyl ring; or

c) an optionally substituted 3 to 8 membered spirocyclic ring containing one to three heteroatoms selected from the group of O, S and N;

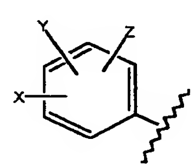
R^A is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, or COR^C;

R^C is H, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, aryl, substituted aryl, C_1 to C_4 alkoxy, substituted C_1 to C_4 alkoxy, C_1 to C_4 aminoalkyl, or substituted C_1 to C_4 aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



X is taken from the group including halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5-membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, $OCOR^D$, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO_2 or NR^5 and containing one or two independent substituents from the group including H, halogen, CN, NO_2 and C_1 to C_3 alkyl, or C_1 to C_3 alkoxy;

R^5 is H or C_1 to C_3 alkyl;

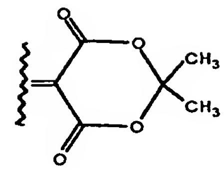
Q is O, S, NR^6, or CR^7R^8;

R^6 is from the group including CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, or SO_2CF_3;

R^7 and R^8 are independent substituents from the group including H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, or CN CO_2R^9;

R^9 is C_1 to C_3 alkyl;

or CR^8R^9 comprise a six membered ring as shown by the structure below



W is O or a chemical bond

or a pharmaceutically acceptable salt thereof.

Further preferred compounds are those of Formula I wherein:

A and B are independent substituents from the group including S, CH or N;

provided that when A is S, B is CH or N; and

when B is S, A is CH or N; and

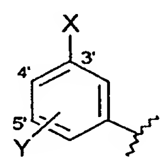
A and B cannot both be CH;

$R^1 = R^2$ and are selected from the group which includes C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 3 to 6 membered spirocyclic ring;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, or COR^C;

R^C is H, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy;

R^4 is a disubstituted benzene ring containing the substituents X and Y as shown below:

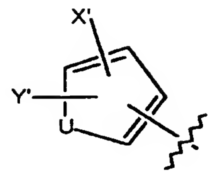


X is selected from the group including halogen, CN, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, or C_1 to C_3 thioalkyl;

Y is a substituent on the 4' or 5' position selected from the group of H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_4 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five membered ring with the structure shown below:



U is O, S, or NR^5;

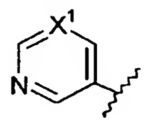
R^5 is H, or C_1 to C_3 alkyl, or C_1 to C_4 CO_2alkyl;

X' is selected from halogen, CN, NO_2, C_1 to C_3 alkyl or C_1 to C_3 alkoxy;

Y' is H or C_1 to C_4 alkyl;

or

R^4 is a six membered ring with the structure:



X^1 is N or CX^2,

X^2 is halogen, CN or NO_2;

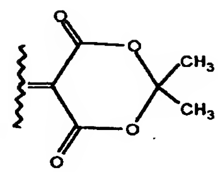
Q is O, S, NR^6, or CR^7R^8;

R^6 is selected from the group including CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, or SO_2CF_3;

R^7 and R^8 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, or CN CO_2R^9;

R^9 is C_1 to C_3 alkyl;

or CR^7R^8 comprise a six membered ring of the structure:



W is O or a chemical bond;

or a pharmaceutically acceptable salt thereof.

Each of the generic and subgeneric groups of compounds herein may further be divided into two further subgroups, one in which Q is oxygen and another wherein Q is selected from S, NR^6, or CR^7R^8.

The compounds of this invention have been shown to bind to the PR and act as agonists and/or antagonists in functional models, either *in-vitro* and/or *in-vivo*. These compounds may be used for contraception, in the treatment of fibroids, endometriosis, breast, uterine, ovarian and prostate cancer, osteoporosis and post menopausal hormone replacement therapy.

The compounds in the present invention contain a pendent aromatic substituent which may consist of aryl, substituted aryl, heteroaryl or substituted heteroaryl groups.

The compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry in Formula I, II, and III, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having from one to 8 carbon atoms, preferably from 1 to 6 carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group having from 2 to 8 carbon atoms, preferably 2 to 6 carbon atoms, with at least one carbon-carbon double bond; "alkynyl" group is intended to

cover both straight- and branched-chain alkyl group having from 2 to 8 carbon atoms, preferably 2 to 6 carbon atoms, with at least one carbon-carbon triple bond.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as just described having one or more substituents from the group including halogen, CN, OH, NO_2, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon of alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

The term "aryl" is used herein to refer to an aromatic system which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include but not limited to phenyl, naphthyl, biphenyl, anthryl, tetrohydronaphthyl, phenanthryl.

The term "substituted aryl" refers to aryl as just defined having one or more substituents from the group including halogen, CN, OH, NO_2, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

The term "heterocyclic" is used herein to describe a stable 4- to 7-membered monocyclic or a stable multicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. The N and S atoms may be oxidized. The heterocyclic ring also includes any multicyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. The heterocyclic ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, for example, tetrahydrofuran, piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and isoquinolinyl.

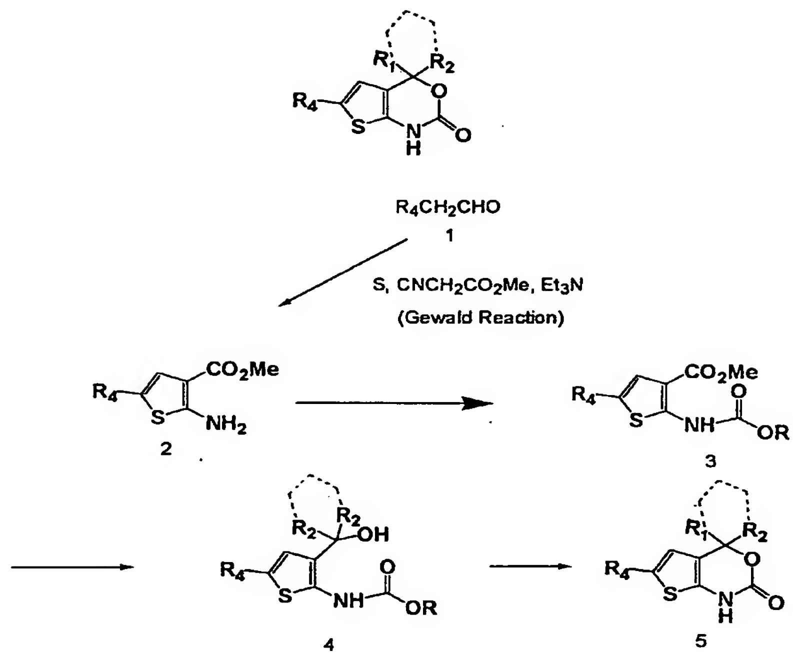
The term "substituted heterocyclic" is used herein to describe the heterocyclic just defined having one or more substituents selected from the group which includes halogen, CN, OH, NO_2, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio. The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl. The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl. The term "alkylcarbonyl" is used herein to refer to the RCO group, where R is alkyl or substituted alkyl. The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl. The term "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or substituted alkyl groups may be either same or different and the point of attachment is on the nitrogen atom. The term "thioalkyl" is used herein to refer to the SR group, where R is alkyl or substituted alkyl. The term "halogen" refers to Cl, Br, F, and I element.

The compounds of this invention can be prepared following the Schemes illustrated below:

CYCLOCARBAMATE DERIVATIVES

Processes for preparing thiophene cyclocarbamate derivatives

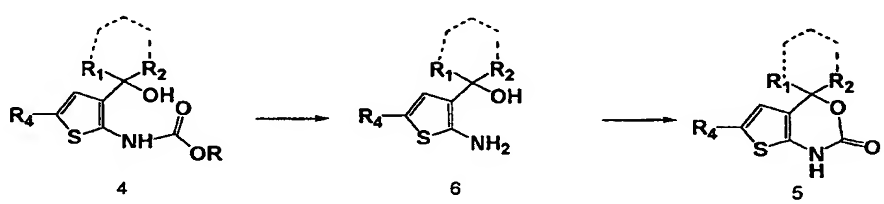
A. Methods for synthesizing the thiophene cyclocarbamate compounds depicted in Scheme 1 are described below:



Scheme 1

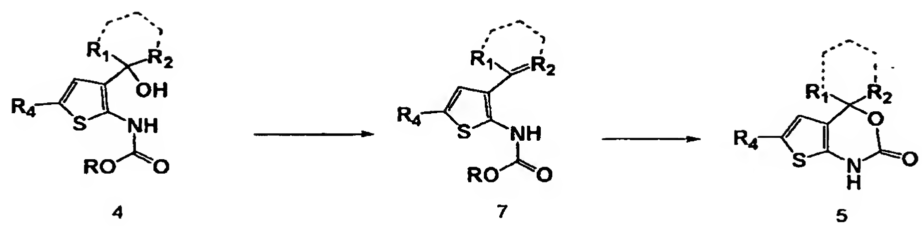
Thus the amino thiophene ester **2** was prepared according to a literature procedure involving the Gewald reaction (see Comprehensive Heterocyclic Chemistry II. A Review of the Literature 1982-1995. A.R. Katritsky et al. Vol. 2 page 639), i.e. the reaction of a suitably substituted aromatic acetaldehyde with sulfur and methyl cyanoacetate in refluxing methanol (Scheme 1). Reaction of the 2-amino group with a suitable chloroformate or carbonate affords the protected amine **3**. This can be accomplished by allowing **2** to react with a chloroformate or carbonate derivative such as methyl chloroformate, ethyl chloroformate, allyl chloroformate, 2-(trimethylsilyl)ethyl chloroformate or di-tert-butyldicarbonate in a solvent such as benzene, toluene, xylene, dichloromethane, tetrahydrofuran or pyridine. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent and may require the presence of a base such as 4-

dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Treatment of the protected amino compound **3** with an organo-metallic reagent such as a Grignard reagent, an alkyl or aryl-zinc reagent, an alkyl or aryl lithium reagent in an inert solvent (tetrahydrofuran, diethylether) under an inert atmosphere (nitrogen or argon) at a suitable temperature from 0°C up to reflux temperature of the solvent will then provide the tertiary alcohol **4**. Compound **4** may then be subjected to basic conditions to effect ring closure to give the cyclocarbamate derivative **5**. Suitable conditions would involve treatment of 4 with a base such as potassium hydroxide in a solvent such as ethanol or potassium t-butoxide in a solvent such as tetrahydrofuran. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent.



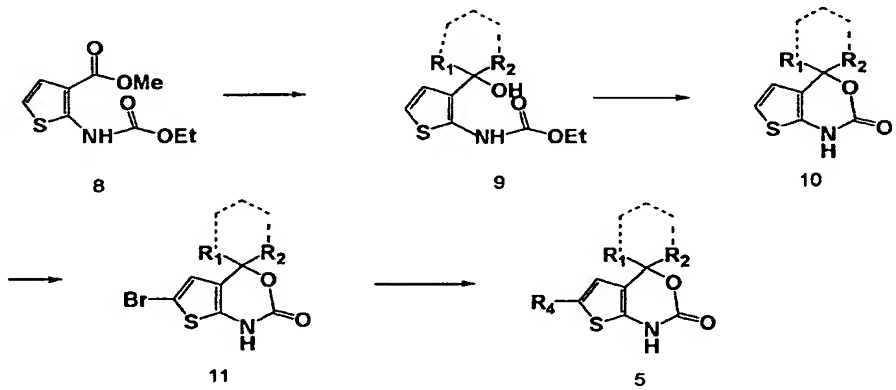
Scheme 2

Alternatively the carbamate protecting group present in **4** may be removed under conditions appropriate for its removal to afford **6** (Scheme 2). Subsequent ring closure of **6** with a reagent such as phosgene, carbonyldiimidazole or dimethyl carbonate in an appropriate solvent (tetrahydrofuran, dichloromethane, benzene, etc.) also will provide access to **5**.



Scheme 3

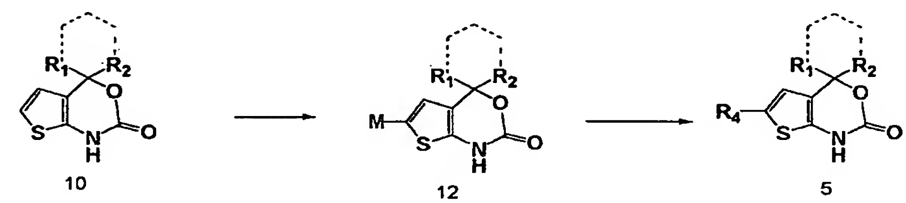
Alternatively, compound **4** may be dehydrated to afford the isopropene derivative **7** (Scheme 3). Suitable conditions for the dehydration would be the use of a reagent such as acetic anhydride, methanesulfonyl chloride, p-toluenesulfonyl chloride or trifluoromethane sulfonyl chloride or anhydride, in a solvent such as pyridine, tetrahydrofuran, dichloromethane or benzene. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent and may require the presence of a base such as 4-dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Exposure of **7** to acidic conditions would then afford ring closure to give **5**. Suitable conditions would be the use of an acid such as p-toluenesulfonic acid, methanesulfonic acid or camphorsulfonic acid in a solvent such as dichloromethane, benzene, toluene or tetrahydrofuran. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent.



Scheme 4

An alternative route to **5** is shown in Scheme **4**. Treatment of the previously described compound **8** (M. Sugiyama, T. Sakamoto, K. Tabata, K. Endo, K. Ito, M. Kobayashi, H. Fukiumi, Chem. Pharm. Bull., 37(8): 2091 (1989)) with an organometallic reagent such as a Grignard reagent, an alkyl or aryl zinc reagent, an alkyl or aryl lithium reagent in an inert solvent (tetrahydrofuran, diethylether) under an inert atmosphere (nitrogen or argon) at a suitable temperature from 0° C up to reflux temperature of the solvent will then provide the tertiary alcohol **9**. Compound **9** may then be subjected to basic conditions to effect ring closure to give the cyclocarbamate derivative **10**. Suitable conditions would involve treatment of **10** with a base such as potassium hydroxide in a solvent such as ethanol or potassium t-butoxide in a solvent such as tetrahydrofuran. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent. Compound **10** may then be converted to the brominated derivative **11**. Suitable conditions would be treatment with bromine or N-bromosuccinimide in a solvent such as dichloromethane, tetrahydrofuran or acetic acid. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent in the presence of an additive such as silica gel. Subsequent reaction of **11** with an aryl or heteroaryl boronic acid, boronic acid anhydride or trialkyl stannane then provides access to the desired biaryl compound **5**. The reaction can be carried

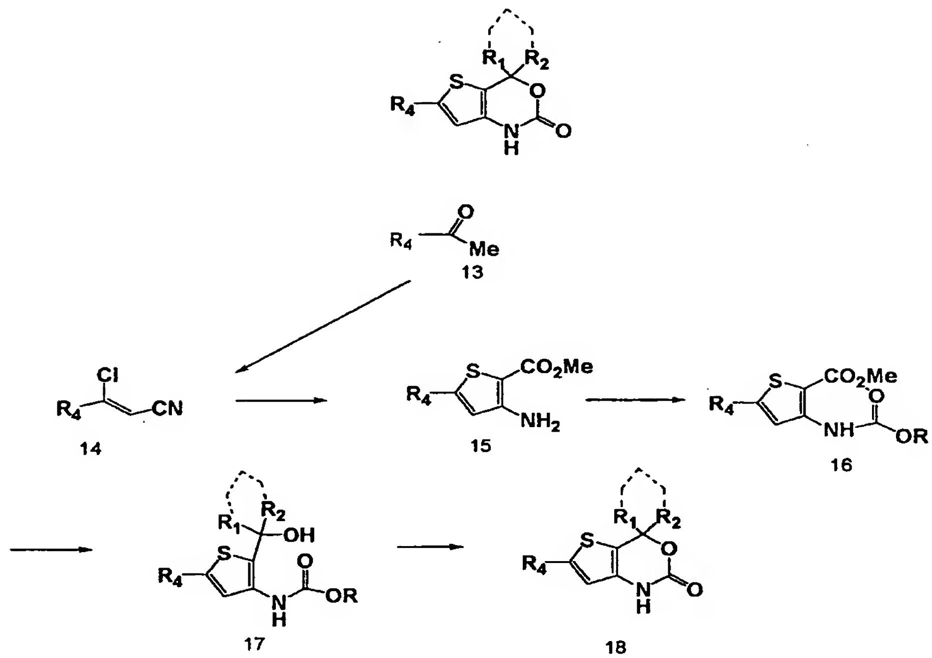
out in a solvent such as acetone, ethanol, benzene, toluene or tetrahydrofuran, under an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent, in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate.



Scheme 5

Alternatively, **10** (Scheme 5) may be treated at low temperature with a reagent such as an alkyl lithium or lithium amide in an inert solvent such as tetrahydrofuran, and then converted to a boronic acid **12** (M= $B(OH)_2$) under the action of trimethyl or triisopropyl borate, or into a stannane via reaction with trimethyltin chloride or bis(trimethyltin). Subsequent reaction of **12** with an aryl or heteroaryl bromide or iodide in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate, would then effect conversion into the desired thiophene cyclocarbamate **5**.

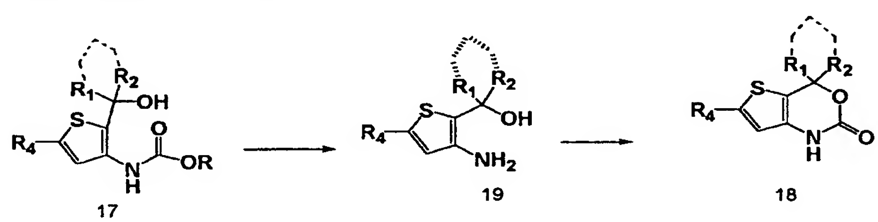
B. Methods for synthesizing the thiophene cyclocarbamate compounds depicted in Scheme 6 are described below:



Scheme 6

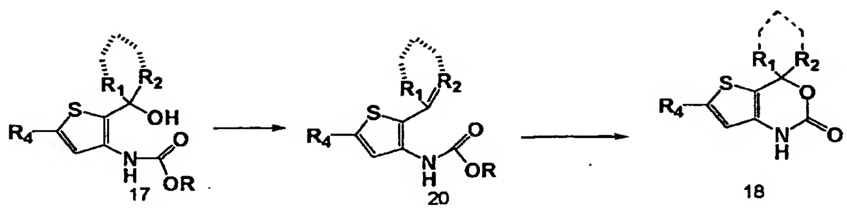
The amino thiophene compounds **15** (Scheme 6) are prepared according to a literature procedure (Comprehensive Heterocyclic Chemistry II. A Review of the Literature 1982-1995. A.R. Katrisky et al., Vol. 2, page 639) which involves treating a suitably substituted aromatic methyl ketone **13** with phosphorus oxychloride in N,N-dimethyl formamide to afford the chloro cyano olefin derivative **14.** Allowing **14** to react with methyl mercaptoacetate in methanol containing sodium methoxide affords the key aminothiophene carboxylate starting material. Reaction of the 2-amino group with a suitable chloroformate or carbonate affords the protected amine **16**. This can be accomplished by allowing **15** to react with a chloroformate or carbonate derivative such as methyl chloroformate, ethyl chloroformate, allyl chloroformate, 2-(trimethylsilyl)ethyl chloroformate or di-tert-butyldicarbonate in a solvent such as benzene, toluene, xylene, dichloromethane, tetrahydrofuran or pyridine. The reaction

can be carried out under an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent and may require the presence of a base such as 4-dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Treatment of the protected amino compound **16** with an organo-metallic reagent such as a Grignard reagent, an alkyl or aryl-zinc reagent, an alkyl or aryl lithium reagent in an inert solvent (tetrahydrofuran, diethylether) under an inert atmosphere (nitrogen or argon) at a suitable temperature from 0° C up to reflux temperature of the solvent will then provide the tertiary alcohol **17**. Compound **17** may then be subjected to basic conditions to effect ring closure to give the cyclocarbamate derivative **18**. Suitable conditions would involve treatment of 4 with a base such as potassium hydroxide in a solvent such as ethanol or potassium t-butoxide in tetrahydrofuran. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent.



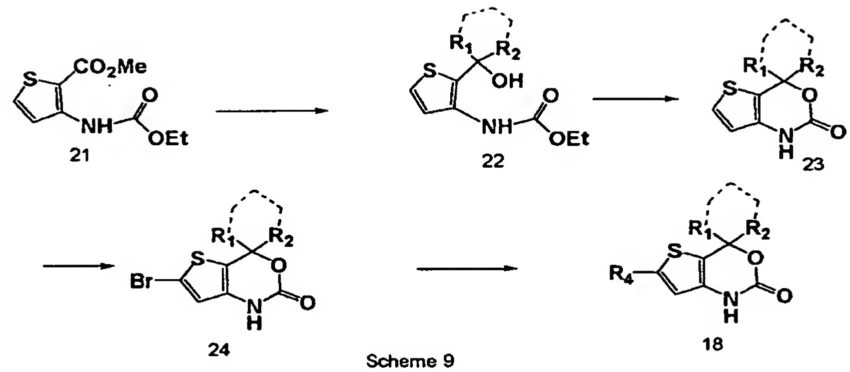
Scheme 7

Alternatively the carbamate protecting group present in **17** may be removed under conditions appropriate for its removal to afford **19** (Scheme 7). Subsequent ring closure of **19** with a reagent such as phosgene, carbonyldiimidazole or dimethyl carbonate in an appropriate solvent (tetrahydrofuran, dichloromethane, benzene, etc.) also will provide access to **18**.



Scheme 8

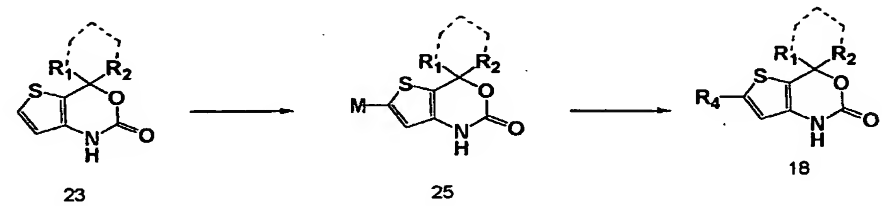
Alternatively, compound **17** may be dehydrated to afford the isopropene derivative **20** (Scheme 8). Suitable conditions for the dehydration would be the use of a reagent such as acetic anhydride, methanesulfonyl chloride, p-toluenesulfonyl chloride or trifluoromethane sulfonyl chloride or anhydride, in a solvent such as pyridine, tetrahydrofuran, dichloromethane or benzene. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent and may require the presence of a base such as 4-dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Exposure of **20** to acidic conditions would then afford ring closure to give **18**. Suitable conditions would be the use of an acid such as p-toluenesulfonic acid, methanesulfonic acid or camphorsulfonic acid in a solvent such as dichloromethane, benzene, toluene or tetrahydrofuran. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0°C up to the reflux temperature of the solvent.



Scheme 9

An alternative route to **18** is shown in Scheme **9**. Treatment of the previously described compound **21**, as taught by H. Fukiumi, M. Sugiyama, T. Sakamoto, Chem. Pharm. Bull., 37(5):1197 (1989), with an organo-metallic reagent such as a Grignard reagent, an alkyl or aryl zinc reagent, an alkyl or aryl lithium reagent in an inert solvent (tetrahydrofuran, diethylether) under an inert atmosphere (nitrogen or argon) at a suitable temperature from 0° C up to reflux temperature of the solvent will then provide the tertiary alcohol **22**. Compound **22** may then be subjected to basic conditions to effect ring closure to give the cyclocarbamate derivative **23**. Suitable conditions would involve treatment of **22** with a base such as potassium hydroxide in a solvent such as ethanol or potassium t-butoxide in tetrahydrofuran. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent. Compound **23** may then be converted to the brominated derivative **24**. Suitable conditions would be treatment with bromine or N-bromosuccinimide in a solvent such as dichloromethane, tetrahydrofuran or acetic acid. The reaction can be carried out in an inert atmosphere (nitrogen or argon) from 0° C up to the reflux temperature of the solvent in the presence of an additive such as silica gel. Subsequent reaction of **24** with an aryl or heteroaryl boronic acid boronic acid anhydride or trialkyl stannane then provides access to the desired biaryl compound **18**. The reaction can be carried out in a solvent such as acetone, ethanol, benzene, toluene or tetrahydrofuran, under an inert atmosphere (nitrogen or argon)

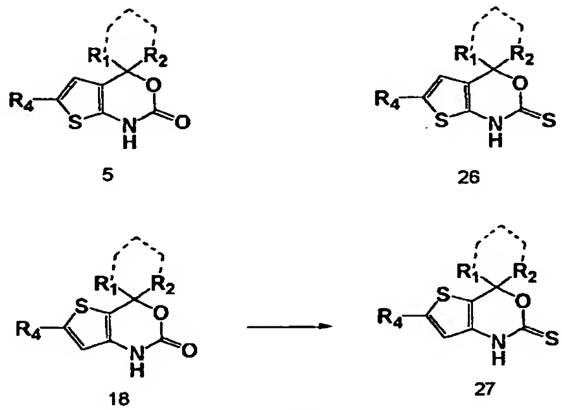
from 0° C up to the reflux temperature of the solvent, in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate.



Scheme 10

Alternatively, **23** (Scheme 10) may be treated at low temperature with a reagent such as an alkyl lithium or lithium amide in an inert solvent such as tetrahydrofuran, and then converted to a boronic acid **25** (M= $B(OH)_2$) under the action of trimethyl or triisopropyl borate, or into a stannane via reaction with trimethyltin chloride or bis(trimethyltin). Subsequent reaction of **25** with an aryl or heteroaryl bromide or iodide in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate, would then effect conversion into the desired thiophene cyclocarbamate **18**.

C. Method for synthesizing the thiophene thiocyclocarbamate compounds **26** and **27** depicted in Scheme 11 are described below:

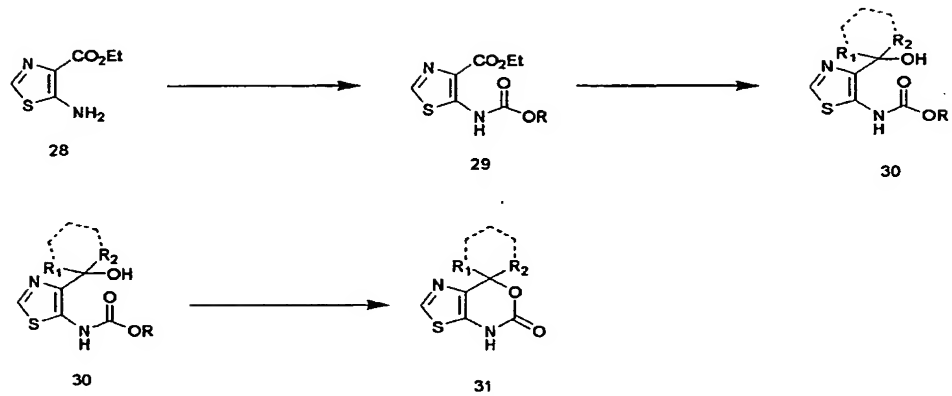


Scheme 11

Thiophene thiocyclocarbamates **26** and **27** may be obtained directly by treating **5** and **18** respectively with phosphorus pentasulfide in refluxing pyridine. Alternatively **5** and **18** may be treated with Lawesson's reagent ([2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide]) in refluxing pyridine to afford **26** and **27**, respectively.

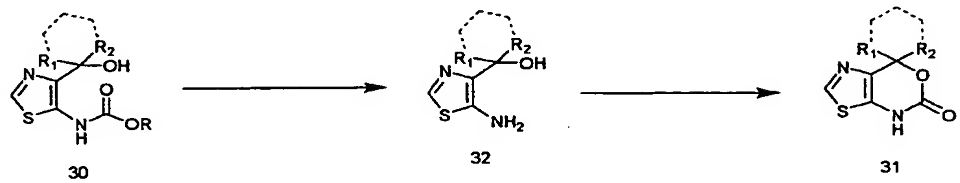
Process for making thiazole cyclocarbamate derivatives.

Methods for preparing the thiazole cyclocarbamate compounds are described below.



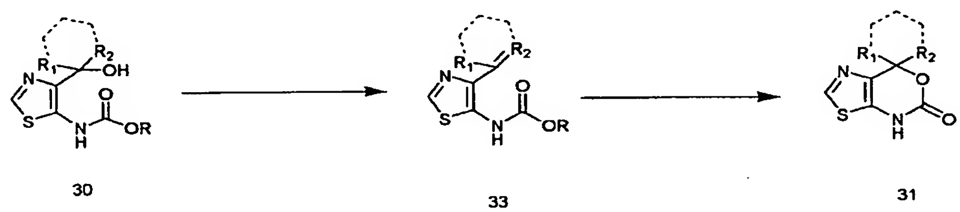
Scheme 12

Thus the thiazole **28** was prepared according to a literature procedure, scheme12 by B. Golankiewicz and P. Januszczyk, *Tetrahedron*, **41**:5989 (1985). Reaction of the amine **28** with a suitable chloroformate or carbonate then gives the protected amine **29**. This may be accomplished by reacting compound **28** with a chloroformate or carbonate derivative such as methylchloroformate, ethylchloroformate, allylchloroformate, 2-(trimethylsilyl)ethylchloroformate or di-tert-butyldicarbonate in a solvent such as dichloromethane, THF, benzene, xylene or pyridine. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent and may require the presence of a base such as 4-dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Exposure of compound **29** to an organo-metallic reagent such as a Grignard reagent, an alkyl or aryl-zinc reagent, an alkyl or aryl lithium reagent in an inert solvent (THF, diethyl ether) under an inert atmosphere (nitrogen or argon) at a suitable temperature from 0 °C up to the reflux temperature of the solvent will then provide the alcohol **30**. Compound **30** may then be exposed to basic conditions to effect ring closure to give the cyclocarbamate derivative **31**. Suitable conditions would involve treatment of compound **30** with a base such as potassium hydroxide in a solvent such as ethanol. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent.



Scheme 13

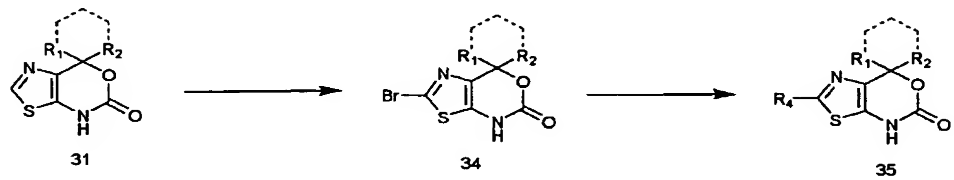
Alternatively the carbamate protecting group present in compound **30** may be removed under conditions appropriate for its removal to afford compound **32** as taught by T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, second ed., Wiley-Interscience (1991). Subsequent ring closure of compound **32** with a reagent such as phosgene, carbonyl diimidazole or dimethyl carbonate in an appropriate solvent (THF, dichloromethane, benzene, etc) will also provide access to compound **31**.



Scheme 14

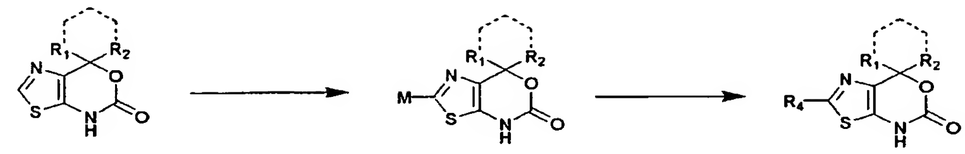
Alternatively, if compound **30** is a tertiary alcohol then it may be dehydrated to afford the isopropene derivative **33**, scheme 3. Suitable conditions for the dehydration would the use of a reagent such as acetic anhydride, methanesulfonyl chloride, p-toluenesulfonyl chloride or trifluoromethane sulfonyl chloride or anhydride, in a solvent such as pyridine, THF, dichloromethane or benzene. The reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent and may require the presence of a base such as

4-dimethylaminopyridine, triethylamine, pyridine or di-isopropyl ethylamine. Exposure of compound **33** to acidic conditions would then afford ring closure to give compound **31**. Suitable conditions would be the use of an acid such as p-toluenesulfonic acid, methanesulfonic acid or camphorsulfonic acid in a solvent such as dichloromethane, benzene, toluene or THF and the reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent.



Scheme 15

Compound **31** may then be converted into the bromide **34**, scheme 15. Suitable conditions would be exposure to bromine or N-bromosuccinimide in a solvent such as dichloromethane, THF or acetic acid, the reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent in the presence of an additive such as silica gel. Subsequent reaction of compound **34** with an aryl or heteroaryl boronic acid, boronic acid anhydride or trialkyl stannane then provides access to the desired biaryl compound **35**. The reaction can be carried out in a solvent such as acetone, ethanol, benzene, toluene or THF, under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent, in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate.



31 36 35

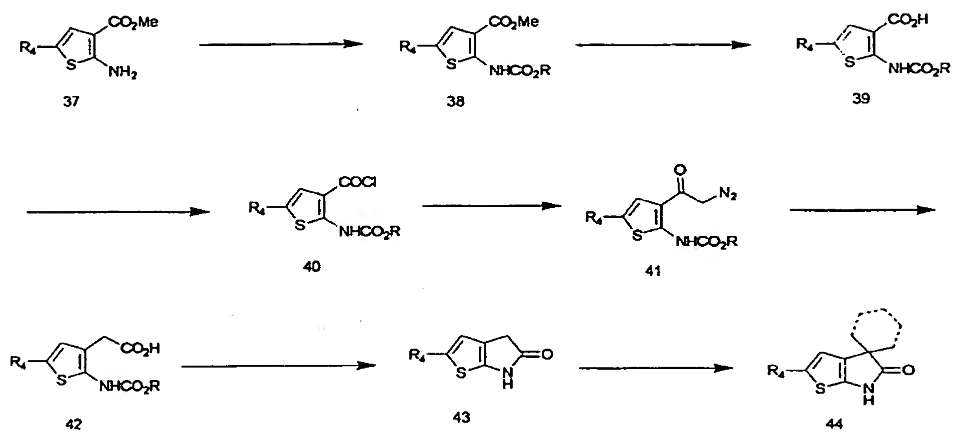
Scheme 16

Alternatively compound **31** may be treated at low temperature with a reagent such as an alkyl lithium or lithium amide in an inert solvent such as THF, and then converted into a boronic acid ($M = B(OH)_2$) **36** under the action of trimethyl or triisopropyl borate, or into a stannane under the action of trimethyltin chloride or bis(trimethyltin), Scheme 16. Subsequent reaction with an aryl or heteroaryl bromide or iodide in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate would then effect conversion into the desired compound **35**.

AMIDE DERIVATIVES

Process for making amide thiophene derivatives.

A method for preparing thiophene derivatives is described below, scheme 17.



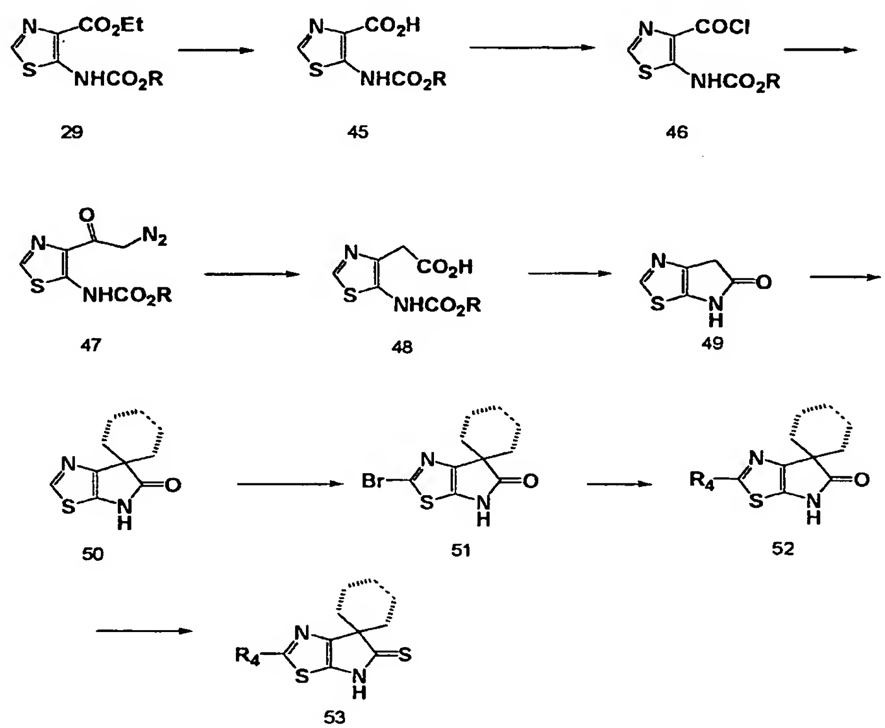
Scheme 17

Thus the amine **37** is converted into a carbamate, such as a *tert*-butyl carbamate as described in scheme 1 for the preparation of compound 2. Hydrolysis of the ester **38** under basic conditions, for example lithium or sodium hydroxide in THF or methanol at room temperature then gives the acid **39**. Conversion of the acid **39** into the acid chloride **40** is accomplished under standard conditions, thionyl chloride or oxalyl chloride either neat or in the presence of a solvent such as dichloromethane and an additive such as a catalytic amount of N,N-dimethylformamide. Compound **40** is then reacted with diazomethane or trimethylsilyldiazomethane in an inert solvent such as THF or dichloromethane, and the product diazoketone **41** is then rearranged in the presence of silver (I) oxide to afford the acid **42**. Treatment of compound **42** under conditions that specifically remove the protecting carbamate functionality, for example acidic conditions, will then affect cyclization to give compound **43**. Reaction of compound **43** with an alkylating agent such as an alkyl iodide, bromide, tosylate or mesylate, or a bis-alkyl iodide, bromide, tosylate or mesylate, under basic conditions, for example butyl lithium in the presence of N,N,N,N-tetramethylene diamine in a solvent such as THF under an inert atmosphere (nitrogen or argon) at a temperature

between -78 °C and the boiling point of the solvent, will then afford the alkylated derivative **44**.

Process for making thiazole derivatives.

A method for preparing thiazole derivatives is described below, scheme 18.



Scheme 18

Hydrolysis of the ester **29** under basic conditions, for example lithium or sodium hydroxide in THF or methanol at room temperature then gives the acid **45**. Conversion of the acid **45** into the acid chloride **46** is accomplished under standard

conditions, for example thionyl chloride or oxalyl chloride either neat or in the presence of a solvent such as dichloromethane and an additive such as a catalytic amount of N,N-dimethylformamide. Compound **46** is then reacted with diazomethane or trimethylsilyldiazomethane in an inert solvent such as THF or dichloromethane, and the product diazoketone **47** is then rearranged in the presence of silver (I) oxide to afford the acid **48**. Treatment of compound **48** under conditions that specifically remove the protecting carbamate functionality, for example acidic conditions, will then affect cyclization to give the heterocycle **49**. Reaction of compound **49** with an alkylating agent such as an alkyl iodide, bromide, tosylate or mesylate, or a bis-alkyl iodide, bromide, tosylate or mesylate, under basic conditions, for example butyl lithium in the presence of N,N,N,N-tetramethylene diamine in a solvent such as THF under an inert atmosphere (nitrogen or argon) at a temperature between -78 °C and the boiling point of the solvent, will then afford the alkylated heterocycle **50**. Compound **50** may then be converted into the bromide **51**. Suitable conditions would be exposure to bromine or N-bromosuccinimide in a solvent such as dichloromethane, THF or acetic acid, the reaction can be carried out under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent in the presence of an additive such as silica gel. Subsequent reaction of compound **51** with an aryl or heteroaryl boronic acid, boronic acid anhydride or trialkyl stannane then provides access to the desired biaryl compound **52**. The reaction can be carried out in a solvent such as acetone, ethanol, benzene, toluene or THF, under an inert atmosphere (nitrogen or argon) from 0 °C up to the reflux temperature of the solvent, in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium (0) or palladium acetate and may require an additive such as sodium carbonate, cesium fluoride or potassium phosphate. The thione derivative, compound **53**, may be obtained directly by treating **52** with phosphorus pentasulfide in refluxing pyridine. Alternatively **52** may be treated with Lawesson's reagent in refluxing pyridine to afford **53**.

The compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include, but are not limited to, the following salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium in the form of esters, carbamates and other conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety *in vivo.*

This invention includes pharmaceutical compositions and treatments which comprise administering to a mammal a pharmaceutically effective amount of one or more compounds as described above wherein Q is oxygen as antagonists of the progesterone receptor. The invention further provides comparable methods and compositions which utilize one or more compounds herein wherein Q is S, NR^6, or CR^7R^8 as agonists of the progesterone receptor.

The progesterone receptor antagonists of this invention, used alone or in combination, can be utilized in methods of contraception and the treatment and/or prevention of benign and malignant neoplastic disease. Specific uses of the compounds and pharmaceutical compositions of invention include the treatment and/or prevention of uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma and other hormone-dependent tumors. Additional uses of the present progesterone receptor antagonists include the synchronization of the estrus in livestock.

The progesterone receptor agonists of this invention, used alone or in combination, can be utilized in methods of contraception and the treatment and/or prevention of dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate. Additional uses of the invention include stimulation of food intake.

This invention also includes pharmaceutical compositions comprising one or more compounds of this invention with a pharmaceutically acceptable carrier or excipient. When the compounds are employed for the above utilities, they may be combined with one or more pharmaceutically acceptable carriers or excipients, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 500 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in a sustained release form. For most large mammals, the total daily dosage is from about 1 to 100 mg, preferably from about 2 to 80 mg. Dosage forms suitable for internal use comprise from about 0.5 to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible

oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvents customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringe ability exits. It must be stable under conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The following non-limiting examples are illustrative of exemplary compound **5.**

EXAMPLE 1

6-(3-chlorophenyl)-1,4-dihydro-4,4-dimethyl-2H-thieno[2,3-d][1,3]oxazine-2-one

2-(3-Chlorobenzyl)acetaldehyde

To a 25°C solution of 3-chlorostyrene in anhydrous CH_2Cl_2 (10.0g, 72.15 mmol) was added a well-stirred solution of $Pb(OAc)_4$ (35.2g, 79.4mmol) in trifluoroacetic acid (150mL), dropwise. The reaction was completed within 30 min of the addition and after being stirred for a further 30 min, the mixture was poured into water, extracted with ether (3X), the combined organic layers were washed with saturated $NaHCO_3$ solution, water, dried ($MgSO_4$), and concentrated to a volume of about 15 ml and immediately used for the following reaction described below.

2-Amino-5-(3-chloro-phenyl)-thiophene-3-carboxylic acid methyl ester

To the crude aldehyde, prepared above, in methanol was added a mixture of sulfur (2.55g, 79.44mmol), methylcyanoacetate (7.88 g, 79.44 mmol), morpholine (6.92g, 79.44) and the resulting reaction mixture was refluxed for 16 hours. The unreacted sulfur was filtered off and the filtrates were evaporated leaving behind a black residue. This residue was extracted with ether and washed with H_2O. Crystallized from ether/hexane (1:5) to obtain white crystals (3.85g, 14.3mmol, 50%), mp 85-87°. ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 3H), 7.18-7.27 (m, 1H), 7.31-7.42 (m, 3H), 7.53 (s, 1H), 7.62 (s, 1H); MS(+APCI) m/z268(M+H); Anal. Calc. For $C_{12}H_{10}ClNO_2S$: C, 53.83, H, 3.76, N, 5.23. Found: C, 53.57, H, 3.37, N, 5.00.

2-Allyloxycarbonylamino-5-(3-chloro-phenyl)-thiophene-3-carboxylic acid methyl ester

To a solution of 2-amino-5-(3-chloro-phenyl)-thiophene-3-carboxylic acid methyl ester (2g, 7.5 mmol) in anhydrous 1,2-dichloroethane (50 mL) was added at room temperature under nitrogen allyl chloroformate (1.6 mL, 15.1 mmol). The reaction mixture was heated at reflux under nitrogen for 18 hours, cooled to room temperature, and treated with a saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was separated and aqueous layer was extracted with

methylene chloride (3x20 mL). The combined organic layers were washed (brine) and dried ($MgSO_4$). After removal of the solvent, the residue was purified by a flash silica gel column (hexane:ethyl acetate/7:1) to give the subtitled compound as an off-white solid (2.14g, 81%): ^{1}H-NMR (DMSO-d_6) δ 10.2 (s, 1H), 7.73 (t, 1H, J = 1.7 Hz), 7.66 (s, 1H), 7.57 (dt, 1H, J = 7.7, 1.7 Hz), 7.41 (t, 1H, J = 7.7 Hz), 7.34 (dt, 1H, J = 6.8, 1.6 Hz), 6.01 (m, 1H), 5.41 (dd, 1H, J = 7.3, 1.6 Hz), 5.29 (dd, 1H, J = 10.5, 1.3 Hz), 4.74 (d, 2H, J = 5.5 Hz), 3.84 (s, 3H). Anal. Calc. For $C_{16}H_{14}ClNO_4S$: C, 54.63, H, 4.01, N, 3.98. Found: C, 54.56, H, 3.92, N, 3.89.

To a solution of 2-allenoxycarbonylamino-5-(3-chloro-phenyl)-thiophene-3-carboxylic acid methyl ester (0.1g, 0.28 mmol) in anhydrous THF was added a solution of methylmagnesium bromide (3.0 M in diethyl ether, 1.5 mL, 4.5 mmol) at room temperature under nitrogen. After stirring at room temperature under nitrogen for 20 minutes, the reaction mixture was treated with brine (10 mL) followed by addition of an aqueous 1N HCl solution (5 mL). Ethyl acetate (20 mL) was added and organic layer was separated, washed with brine (5 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by a flash column (silica gel, hexane:ethyl acetate/5:1) to give carbinol which was used in next step without further purification and characterization.

A mixture of above crude carbinol, potassium hydroxide (excess) in ethanol was stirred at room temperature under nitrogen overnight. The reaction solution was then acidified by an addition of a cold aqueous 1N HCl solution. Ethyl acetate (20 mL) was added and organic layer was separated, washed with brine (5 mL) and dried ($MgSO_4$). After removal of the solvent, the residue was purified by a silica gel column (hexane:ethyl acetate/2:1) to give the title compound as an off-white solid (16 mg, 19% for two steps): mp 149-150 °C; ^{1}H-NMR (DMSO-d_6) δ 10.69 (s, 1H), 7.64 (t, 1H, J = 1.8 Hz), 7.49 (s, 1H), 7.47 (dt, 1H, J = 7.7, 1.4 Hz), 7.39 (t, 1H, J = 7.8 Hz), 7.29 (dt, 1H, J = 7.8, 1.3 Hz), 1.61 (s, 6H). MS (EI) m/z 293/295 (M^+). Anal. Calc. For $C_{14}H_{12}ClNO_2S$: C, 57.24, H, 4.12, N, 4.77. Found: C, 57.27, H, 4.25, N, 4.66.

EXAMPLE 2

6-(3-chlorophenyl)-1,4-dihydro-4,4-dimethyl-2H-thieno[3,2-d][1,3]oxazine-2-one

3-Chloro-3-(3-chloro-phenyl)-acrylonitrile

A solution of $POCl_3$ was slowly added to anhydrous DMF over a period of 20 minutes and the temperature was maintained around 30°C. 3'-Chloroacetophenone solution in anhydrous DMF was added to the above solution and the reaction temperature was allowed to rise to around 50°C. Hydroxylamine HCl was added to the reaction solution, portionwise, over 1 hour. A volume of 500 mL of water was added to form precipitate, stirred for 1 hour and precipitate was collected on a Büchner funnel, washed with H_2O, and dried to afford a yellow crystalline compound, mp 60-62°C. ^1H NMR (DMSO-d_6) δ 1.60(s, 6H), 7.30 (d, 1H, J = 8.41Hz), 7.41(d, 1H, J = 8.41Hz), 10.47 (s, 1H); MS(+APCI)m/z 213(M+H); Anal. Calc. For $C_9H_9ClN_2O_2$: C, 50.84, H, 4.27, N, 13.17. Found: C, 50.99, H, 4.28, N, 12.98.

3-Amino-5-(3-chloro-phenyl)-thiophene-2-carboxylic acid methyl ester

Sodium pellets were slowly added to methanol solution to form NaOMe in situ, then methyl thioglycolate was added over a period of 20 minutes to the methanol solution. A solution of 3-Chloro-3-(3-chloro-phenyl)-acrylonitrile in methanol was added slowly and was brought to reflux for 1 hour. The reaction mixture was cooled to room temperature and methanol was concentrated to 100 mL and 200 mL of water was added, stirred for 30 minutes and the yellow precipitate was collected and washed with water several times to yield a yellow crystalline compound, mp 92-95°C. ^1H NMR (DMSO-d_6) δ 1.60 (s, 6H), 7.30 (d, 1H, J = 8.41Hz), 7.41(d, 1H, J = 8.41Hz), 10.47 (s, 1H); MS(+APCI)m/z 213(M+H); Anal. Calc. For $C_9H_9ClN_2O_2$: C, 50.84, H, 4.27, N, 13.17. Found: C, 50.99, H, 4.28, N, 12.98.

3-Allyloxycarbonylamino-5-(3-chloro-phenyl)-thiophene-2-carboxylic acid methyl ester

To a solution of 3-Amino-5-(3-chloro-phenyl)-thiophene-2-carboxylic acid methyl ester (15g, 56.0mmol) in toluene (200mL) was added a solution of allyl

chloroformate (8.10g, 67.2mmol) in toluene (5.0mL) and the resulting reaction solution was heated under reflux for 3 h. Toluene was stripped down and the crystals were collected and washed with ether/hexane to afford a yellow crystalline compound, mp 101-103°C. ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H), 4.68-4.71 (d, 2H, J = 5.46Hz), 5.26-5.30 (dd, 1H, J = 1.35, 9.84Hz), 5.36-5.42 (dd, 1H, J = 1.57, 15.68Hz), 5.96(m, 2H), 7.50-7.52 (m, 2H), 7.67-7.71 (m, 1H), 7.79 (s, 1H), 8.10 (s, 1H); MS(+APCI) m/z 352(M+H); Anal. Calc. For $C_{16}H_{14}ClNO_4S$: C, 54.63, H, 4.01, N, 3.97. Found: C, 54.05, H, 4.17, N, 3.84.

[5-(3-Chloro-phenyl)-2-(1-hydroxy-1-methyl-ethyl)-thiophen-3-yl]-carbamic acid allyl ester

To a solution of 3-Allyloxycarbonylamino-5-(3-chloro-phenyl)-thiophene-2-carboxylic acid methyl ester (5.3g, 15.1mmol) in anhydrous THF (30mL) at room temperature was added a solution of 3.0M MeMgI in ether (20.1mL, 60.24mmol). After 30 minutes, the reaction was slowly quenched with H_2O (10mL), treated with saturated NH_4OH (100mL), extracted with ether (200mL), washed with brine, dried ($MgSO_4$), concentrated, and chromatographed (hexane/ether, 1:4): mp 60-61 °C; ^{1}H NMR (DMSO-d_6) δ 1.52 (s, 6H), 4.59-4.61 (d, 2H, J = 5.35Hz), 5.22-5.36 (m, 2H), 5.91-6.04 (m, 2H), 7.33-7.67 (m, 5H), 8.89 (s, 1H); MS(EI) m/z 351/353(M+H); Anal. Calc. For $C_{17}H_{18}ClNO_3S$: C, 58.03, H, 5.16, N, 3.98. Found: C, 58.17, H, 5.16, N, 3.97.

6-(3-Chlorophenyl)-1,4-dihydro-4,4-dimethyl-2H-thieno[3,2-d][1,3]oxazin-2-one

To a solution of [5-(3-Chloro-phenyl)-2-(1-hydroxy-1-methyl-ethyl)-thiophen-3-yl]-carbamic acid allyl ester (.12g, .34mmol) in anhydrous THF (5.0mL) was added KO^{t}Bu (0.076g, 0.068mmol) and stirred for 15 minutes, quenched with H_2O, and in situ crystallization was carried out by adding minimal amount of MeOH to the solution. The white crystals were collected on a Büchner funnel, mp 123-125°C. ^{1}H NMR (DMSO-d_6) δ 1.64(s, 6H), 7.05(s, 1H), 7.37-7.48(m, 2H), 7.53-7.56(s, 1H),

7.67-7.68 (m,1H), 10.41(s, 1H); MS(EI) m/z 293/295(M+H); Anal. Calc. For $C_{17}H_{18}ClNO_3S$: C, 57.24, H, 4.12, N, 4.77. Found: C, 56.93, H, 3.92, N, 4.97.

Example 3 - Pharmacology

The progestational activity of the current invention was evaluated in the PRE-luciferase assay in CV-1 cells, described below. *In-vitro* potencies can be in the range 0.01nM-10,000nM. *In vivo* potencies are anticipated to be in the range 1 mg/kg to 30 mg/kg.

The object of this assay is to determine a compound's progestational or antiprogestational potency based on its effect on PRE-luciferase reporter activity in CV-1 cells co-transfected with human PR and PRE-luciferase plasmids. The materials methods used in the assay are as follows.

a. Medium: The growth medium was as follows: DMEM (BioWhittaker) containing 10% (v/v) fetal bovine serum (heat inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL). The experimental medium was as follows: DMEM (BioWhittaker), phenol red-free, containing 10% (v/v) charcoal-stripped fetal bovine serum (heat-inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Cell culture, transfection, treatment, and luciferase assay

Stock CV-1 cells are maintained in growth medium. Co-transfection is done using $1.2x10^7$ cells, 5 mg pLEM plasmid with hPR-B inserted at Sph1 and BamH1 sites, 10 mg pGL3 plasmid with two PREs upstream of the luciferase sequence, and 50 mg sonicated calf thymus DNA as carrier DNA in 250 ml. Electroporation is carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II. After electroporation, cells are resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 µl. Following overnight incubation, the medium is changed to experimental medium. Cells are then treated with reference or test

compounds in experimental medium. Compounds are tested for antiprogestational activity in the presence of 3 nM progesterone. Twenty-four hr. after treatment, the medium is discarded, cells are washed three times with D-PBS (GIBCO, BRL). Fifty μl of cell lysis buffer (Promega, Madison, WI) is added to each well and the plates are shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase activity is measured using luciferase reagents from Promega.

c. Analysis of Results:

Each treatment consists of at least 4 replicates. Log transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC_{50} or IC_{50} values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear response analyses.

d. Reference Compounds:

Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC_{50} or IC_{50} values are calculated.

Table 1. Estimated EC_{50}, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three individual studies

Compound	Exp.	EC50 (nM)	SE	95% CI lower	95% CI upper
Progesterone	1	0.616	0.026	0.509	0.746
	2	0.402	0.019	0.323	0.501
	3	0.486	0.028	0.371	0.637
Trimegestone	1	0.0075	0.0002	0.0066	0.0085
	2	0.0081	0.0003	0.0070	0.0094
	3	0.0067	0.0003	0.0055	0.0082

Table 2. Estimated IC_{50}, standard error (SE), and 95% confident interval (CI) for the antiprogestin, RU486 from three individual studies

Compound	Exp.	IC 50 (nM)	SE	95% CI lower	95% CI upper
RU486	1	0.028	0.002	0.019	0.042
	2	0.037	0.002	0.029	0.048
	3	0.019	0.001	0.013	0.027

Progestational activity: Compounds that increase PRE-luciferase activity significantly ($p<0.05$) compared to vehicle control are considered active.

Antiprogestational activity: Compounds that decrease 3 nM progesterone induced PRE-luciferase activity significantly ($p<0.05$)

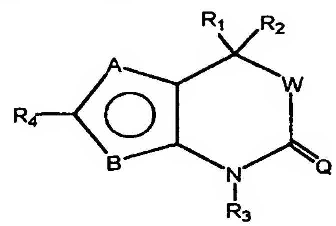
EC_{50}: Concentration of a compound that gives half-maximal increase PRE-luciferase activity (default-nM) with SE.

IC_{50}: Concentration of a compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity (default-nM) with SE.

All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

What is Claimed:

1. A compound of Formula I:



I

wherein:

A and B are independent substituents selected from S, CH or N;

Provided that when A is S, B is CH or N; provided that when B is S, A is CH or N;

and A and B cannot both be CH;

and when A and B both equal N, one N may be optionally substituted with an C_1 to C_6 alkyl group;

R_1 and R_2 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R^1 and R^2 are fused to form:

a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring; or

b) an optionally substituted 3 to 8 membered spirocyclic alkenyl ring; or

c) an optionally substituted 3 to 8 membered spirocyclic ring containing one to three heteroatoms selected from the group of O, S and N;

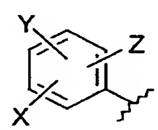
R^A is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, or COR^C;

R^C is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below,



X is selected from halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, $OCOR^D$, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independently selected from H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five or six membered ring with 1, 2, or 3 heteroatoms selected from O, S, SO, SO_2 or NR^5, the five or six membered rings being optionally substituted by one or two independent substituents selected from H, halogen, CN, NO_2 and C_1 to C_3 alkyl, C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, COR^F, or NR^GCOR^F;

R^F is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^G is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^5 is H, or C_1 to C_3 alkyl;

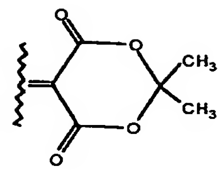
Q is O, S, NR^6, or CR^7R^8;

R^6 is from the group including CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, or SO_2CF_3;

R^7 and R^8 are independent substituents from the group including H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, or CN CO_2R^9;

R^9 is C_1 to C_3 alkyl;

or CR^7R^8 may comprise a six membered ring of the structure below:



W is O or a chemical bond

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein:

A and B are independent substituents S, CH or N,

provided that when A is S, B is CH or N; and

when B is S, A is CH or N; and

A and B cannot both be CH; and

when A and B both equal N, one N may be optionally substituted with an C_1 to C_6 alkyl group;

R^1 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

R^2 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R^1 and R^2 are fused to form:

a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring; or

b) an optionally substituted 3 to 8 membered spirocyclic alkenyl ring; or

c) an optionally substituted 3 to 8 membered spirocyclic ring containing one to three heteroatoms selected from the group of O, S and N;

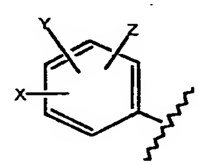
R^A is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, or COR^C;

R^C is H, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, aryl, substituted aryl, C_1 to C_4 alkoxy, substituted C_1 to C_4 alkoxy, C_1 to C_4 aminoalkyl, or substituted C_1 to C_4 aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



X is taken from the group including halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5-membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, $OCOR^D$, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five or six membered ring with 1, 2, or 3 heteroatoms selected from O, S, SO, SO_2 or NR^5, the five or six membered ring being optionally substituted by one or two independent substituents selected from H, halogen, CN, NO_2 and C_1 to C_3 alkyl, or C_1 to C_3 alkoxy;

R^5 is H or C_1 to C_3 alkyl;

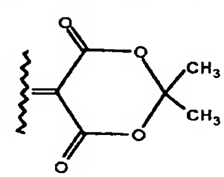
Q is O, S, NR^6, or CR^7R^8;

R^6 is from the group including CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, or SO_2CF_3;

R^7 and R^8 are independent substituents from the group including H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, or CN CO_2R^9;

R^9 is C_1 to C_3 alkyl;

or CR^8R^9 comprise a six membered ring as shown by the structure below



W is O or a chemical bond

or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1 wherein:

A and B are independent substituents from the group including S, CH or N;

provided that when A is S, B is CH or N; and

when B is S, A is CH or N; and

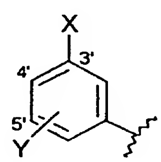
A and B cannot both be CH;

$R^1 = R^2$ and are selected from the group which includes C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 3 to 6 membered spirocyclic ring;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, or COR^C;

R^C is H, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy;

R^4 is a disubstituted benzene ring containing the substituents X and Y as shown below:

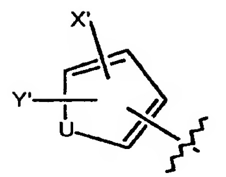


X is selected from the group including halogen, CN, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, or C_1 to C_3 thioalkyl;

Y is a substituent on the 4' or 5' position selected from the group of H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_4 alkyl, or C_1 to C_3 thioalkyl;

or

R^4 is a five membered ring with the structure shown below:



U is O, S, or NR^5;

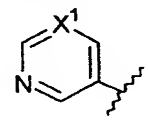
R^5 is H, or C_1 to C_3 alkyl, or C_1 to C_4 CO_2alkyl;

X' is selected from halogen, CN, NO_2, C_1 to C_3 alkyl or C_1 to C_3 alkoxy;

Y' is H or C_1 to C_4 alkyl;

or

R^4 is a six membered ring with the structure:



X^1 is N or CX^2,

X^2 is halogen, CN or NO_2;

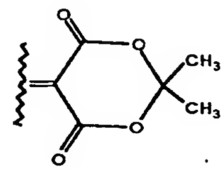
Q is O, S, NR^6, or CR^7R^8;

R^6 is selected from the group including CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, or SO_2CF_3;

R^7 and R^8 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, or CN CO_2R^9;

R^9 is C_1 to C_3 alkyl;

or CR^7R^8 comprise a six membered ring of the structure:



W is O or a chemical bond;

or a pharmaceutically acceptable salt thereof.

4. A compound of Claim 3 wherein:

$R^1 = R^2$ and are selected from the group which includes C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or spirocyclic alkyl constructed by fusing R^1 and R^2 to form a 3 to 6 membered spirocyclic ring;

and A, B, R^3, R^C, R^4, X, Y, U, R^5, X', Y', X^1, X^2, Q, R^6, R^7, R^8, R^9 and W are as defined in Claim 3;

or a pharmaceutically acceptable salt thereof.

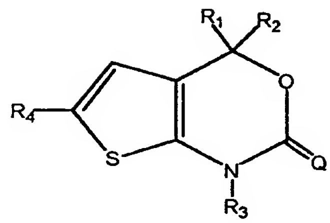
5. A compound of Claim 3 wherein:

R^1 and R^2 are fused to form a 3 to 6 membered spirocyclic ring;

and A, B, R^3, R^C, R^4, X, Y, U, R^5, X', Y', X^1, X^2, Q, R^6, R^7, R^8, R^9 and W are as defined in Claim 3;

or a pharmaceutically acceptable salt thereof.

6. A compound of the formula:



wherein:

R_1 and R_2 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R^1 and R^2 are fused to form:

a) a 3 to 6 membered spirocyclic alkyl ring; or

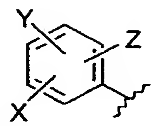
b) a 3 to 6 membered spirocyclic alkenyl ring;

R^3 is H, OH, NH_2, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, or COR^C;

R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^C is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^4 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below,



X is selected from halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2, C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, $OCOR^D$, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl; and

Y and Z are independently selected from H, halogen, CN, NO_2, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl;

or a pharmaceutically acceptable salt thereof.

7. A compound of Claim 1 which is 6-(3-chlorophenyl)-1,4-dihydro-4,4-dimethyl-2H-thieno[2,3-d][1,3]oxazine-2-one, or a pharmaceutically acceptable salt thereof.

8. A method of inducing contraception in a mammal, the method comprising administering to a mammal in need thereof a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

9. A method of treatment or prevention in a mammal of benign or malignant neoplastic disease the method comprising administering to a mammal in need thereof a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

10. The method of Claim 9 wherein the benign or malignant neoplastic disease is selected from uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas or adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma or other hormone-dependent tumors.

11. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 00/11825

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D498/04 A61K31/535 A61P15/18 A61P35/00
//(C07D498/04,333:00,265:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 688 810 A (ZHI LIN ET AL) 18 November 1997 (1997-11-18) cited in the application column 12, line 28 -column 15, line 63; examples 1-3	1-11
A	MAMAEV V P ET AL: "SYNTHESIS OF 4H-THIENO'3,2-B!PYRROL-5(6H)-ONE" BULLETIN OF THE ACADEMY OF SCIENCES OF THE USSR. DIVISION OF CHEMICAL SCIENCE,US,CONSULTANTS BUREAU. NEW YORK, vol. 9, 1966, pages 1549-1553, XP000917791 *compound I*	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 September 2000	28.09.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Härtinger, S

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/11825

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 9-10 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ..tional Application No
PCT/US 00/11825

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5688810 A	18-11-1997	AU 717251 B	23-03-2000
		AU 4597796 A	10-07-1996
		BR 9510486 A	02-06-1998
		CA 2208347 A	27-06-1996
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		HU 78117 A	29-11-1999
		US 5696130 A	09-12-1997
		US 5688808 A	18-11-1997
		US 5693646 A	02-12-1997
		US 5693647 A	02-12-1997
		US 5696127 A	09-12-1997
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		US 5994544 A	30-11-1999